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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kohane *et al.*	Examiner:	Fubara, Blessing M.
Serial No.:	09/981,020	Art Unit:	1615
Filed:	October 16, 2001		
For:	LIPID-PROTEIN-SUGAR PARTICLES FOR DRUG DELIVERY		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Responsive to the final Office Action mailed June 12, 2008, Applicant respectfully requests consideration of this Pre-Appeal Brief Request for Review and requests review of the final rejection in the above-referenced application. Applicant also submits herewith a Notice of Appeal, as required by the guidelines for filing a Pre-Appeal Brief Request for Review (Official Gazette, July 12, 2005). The deadline for responding to the Office Action without fees was September 12, 2008. A three-month extension of time from September 12, 2008, up to and including December 12, 2008, is hereby respectfully requested, and the extension fee of $555.00 under 37 C.F.R. § 1.17(a) for a small entity is being paid via the U.S. Patent and Trademark Office's Electronic Filing System's credit card payment option. Applicant thus submits that the present Request and accompanying Notice of Appeal are timely submitted on Friday, December 12, 2008.

No **Amendments** are being filed with this Request.

Remarks begin on page 2 of this paper.

Remarks

Interview

Applicant thanks the Examiner for a telephone interview that took place on November 6, 2008, during which the present rejections were discussed. Applicant thanks the Examiner for suggesting that Applicant file this Pre-Appeal Brief Request for Review.

Rejection under 35 U.S.C. § 112, for indefiniteness

All pending claims (*i.e.*, claims 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91, and 96-107) stand rejected under 35 U.S.C. § 112, as being indefinite. In particular, the Examiner states that the boundaries of derivatives of cellulose and dextran are not clear. Applicant respectfully disagrees.

The meaning of derivatives of cellulose and dextran is well understood in the art. Indeed, established USPTO practice confirms the definiteness of these terms. A search of the USPTO's database reveals 34,104 issued patents that recite "cellulose derivative(s)" or "derivative(s) of cellulose" in the claims, and 821 issued patents that recite "dextran derivative(s)" or "derivative(s) of dextran" in the claims. Even a cursory review of these results shows that these terms are recited extensively in claims that have been issued by the USPTO. Applicant respectfully submits that the USPTO appreciates that the term derivatives of cellulose and dextran is readily understood by one of ordinary skill in the art and is not indefinite. Applicant requests that this rejection be removed.

Rejection under 35 U.S.C. § 112, for lack of written description

All pending claims (*i.e.*, 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91, and 96-107) stand rejected under 35 U.S.C. § 112, for lack of written description. The Examiner states that the original specification does not describe a microparticle that is not a liposome and does not describe a microparticle that does not include a synthetic polymer. Applicant respectfully disagrees. During an in-person interview that took place on February 4, 2008, the Examiner indicated that the rejection could be overcome by specifically pointing to the specification for support for exclusion of synthetic polymers and liposomes.

Applicant respectfully submits that the specification does describe microparticles that do not include a synthetic polymer. For example, page 3 of the specification describes "a system for

delivering an agent encapsulated in a lipid-protein-sugar matrix to an individual" (lines 8-9). The specification further states, "In another particularly preferred embodiment, a synthetic polymer is substituted for at least one of the components of the LPSPs–lipid, protein, and/or sugar" (page 3, lines 16-18). Page 14 of the specification reiterates this point, stating "The agent is preferably encapsulated in a matrix comprising lipid, protein, and sugar to form microparticles … In other embodiments, a synthetic polymer … is used as a substitute for at least one of the components of the LPSPs [*i.e.* lipid, protein, sugar]" (lines 7-8 and 12-15). Thus, the specification clearly describes LPSPs that do not include a synthetic polymer as distinct from particles which do include a synthetic polymer. Clearly, the inventors at the time of filing envisioned microparticles that do not include a synthetic polymer.

Furthermore, the specification shows that LPSPs which do not include a synthetic polymer are superior to particles which include a synthetic polymer. Specifically, particles containing PLGA were shown to elicit a statistically significant increased inflammatory response at the site of injection compared to lipid-protein-sugar particles (page 52, sections entitled "Tissue reaction two weeks after injection" and "Tissue reaction eight weeks after injection"). In addition, PLGA particles were found at locations where they were not intentionally placed (page 54, section entitled "Other findings on dissection"). There were no similar adverse findings in rats injected with LPSPs. Given the negative consequences of administering a drug via microparticles including a synthetic polymer, the present specification not only describes particles that do not include a synthetic polymer, but also shows the advantages of using a microparticle that does not include a synthetic polymer.

Applicant also respectfully submits that the specification describes microparticles that are not liposomes. As discussed with the Examiner during the in-person interview on February 4, 2008, the methods described in the specification for making microparticles are not methods that can be used to produce liposomes. For example, "spray drying, single and double emulsion solvent evaporation, solvent extraction, phase separation, [and] simple and complex coacervation" (page 23, lines 13-14) are methods that produce solid microparticles, as recited by the present claims. Such methods do not produce liposomes. Therefore, the specification does describe solid microparticles which are not liposomes, as recited in the claims.

For all of the reasons outlined above, recitation of LPSPs which do not include a synthetic polymer and are not liposomes is fully supported by the specification and does not constitute new matter. Applicant, therefore, respectfully requests that the rejection be removed.

Rejection under 35 U.S.C. § 103(a), for obviousness

Claims 1, 7, 12-15, 17-20, 23-25, 27, 30, 37, 47, 48-65, 80, 84, 86-91, 96-99, 101, and 103-107 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). The Examiner states that the particles of the present invention are obvious in view of Bernstein. Applicant disagrees.

The specification of Bernstein does not teach microparticles comprising a lipid, a protein, and a sugar. As acknowledged by the Examiner in the Interview Summary that was mailed after the in-person interview , "While Bernstein lists a number of materials that can form the matrix, Bernstein does not indicate using mixture or blend (*sic*) of those materials for the matrix." Bernstein does include lipids, proteins, and sugars in a list of many different components that can be used to form a polymeric matrix (column 4, lines 19-22). However, Bernstein does not indicate that the specific combination of these three particular components (*i.e.*, lipid, protein, and sugar) should be selected as matrix components. As acknowledged by the Examiner during the interview, there is absolutely no suggestion in Bernstein to "pick and choose" the combination of lipid, protein, and sugar to prepare microparticles, as recited by the present claims.

Moreover, the only microparticles that were actually prepared by Bernstein contain only two components, PLGA (a synthetic polymer) and a lipid. The particles prepared by Bernstein do not contain a sugar or a protein, and the prepared particles always included a synthetic polymer (*i.e.* PLGA). Therefore, Bernstein does not teach or suggest microparticles which do not comprise a synthetic polymer such as PLGA.

Applicant, therefore, submits that the present claims are not rendered obvious by the teachings of Bernstein and respectfully requests that the rejection be removed.

Claims 8-11 and 102 stand rejected by the Examiner under § 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345), further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). The Examiner only cites Goldenheim for teaching an anesthetic as the

agent in the particles. As discussed above, Bernstein does not render obvious the claimed microparticles of the present application, and the combination of Goldenheim and Bernstein also does not teach the claimed microparticles. The claimed microparticles do not include a synthetic polymer but do include a lipid, a protein, and a sugar. Therefore, even if there is a teaching or suggestion to combine Goldenheim and Bernstein, the combination would not render the claimed invention obvious because the references, even when combined, only teach a matrix comprising a synthetic polymer and do not teach microparticles that include a lipid, a protein, and a sugar. Applicant, therefore, respectfully requests that the rejection be removed.

Conclusion

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5215.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

/C. Hunter Baker/
C. Hunter Baker, M.D., Ph.D., J.D.
Registration Number: 46,533

Choate, Hall & Stewart LLP
Two International Place
Boston, MA 02110
t (617) 248-5215
f (617) 502-5002
cbaker@choate.com
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